Article abstract—Eighteen patients with chronic progressive multiple sclerosis (MS) were treated in an open preliminary trial of the interferon inducer and immune modulator, poly ICLC. All patients produced substantial interferon levels and experienced acute side effects, including fever and transient worsening of neurologic symptoms. Of nine patients with rapid neurologic deterioration at the time of entry into the study, only three had disease progression during treatment. We conclude that poly ICLC can be administered safely to MS patients, and that a controlled trial will be necessary to determine efficacy.

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Preliminary trial of poly ICLC in chronic progressive multiple sclerosis

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Interferon (IFN) has been proposed as a treatment for multiple sclerosis (MS) because virus infection may cause MS,[1] and IFN responses may be defective in MS patients.[2] The design of clinical trials has been complicated by the limited availability of IFN, the 30:1 serum to CSF barrier to IFN,[3] the impurity of many IFN preparations, and the molecular heterogeneity of IFN.[4] Different approaches have therefore been used. Impure preparations of alpha and beta IFN have been available in limited quantities, and a few patients with chronic progressive MS were studied in two negative preliminary trials of low doses of either alpha[5] or beta[6] IFN given systemically. In a controlled trial of intrathecally administered beta IFN, a reduced exacerbation rate was reported,[7] but others[8] found placebo as effective as alpha IFN given systemically. Two newer approaches to IFN treatment, administration of IFN produced by recombinant DNA technology and systemically administered IFN-inducing agents, offer advantages, but have not been used in MS.

Poly ICLC, a potent IFN inducer, has been cleared for investigational use. Administration of the substance stimulates high IFN levels in serum[9] and CSF,[10] including multiple subspecies of alpha and lesser amounts of beta (H.B. Levy, unpublished observations). In cancer patients, the drug has been well tolerated.[10] A preliminary trial of poly ICLC in chronic progressive MS has been conducted following established guidelines[11] with the following specific goals: (1) the safety of poly ICLC in MS patients was assessed; (2) methods of administration had to be developed to deal with temperature elevations and other side effects; (3) the ability of poly ICLC to stimulate clinically useful levels of IFN in MS patients was investigated; and (4) using each patient as his own control, disease progression was compared before, during, and after a course of treatment to establish if further study to determine efficacy was warranted.

Methods. *Patients.* Nine men and nine women, aged 23 to 57, with definite MS[12] and chronic progressive[11] symptoms (table 1) were studied. Patients with relapsing-remitting disease were excluded, except for one patient (# 5) who had a progressive course with periods of worsening associated with steroid withdrawal. Patients with complicating medical illnesses and those who had received immunosuppressives other than steroids were excluded. Patients with a spectrum of disease durations (2 to 20 years), disease severities (DSS 3 to 9), and rates of progression were included. Course before, during, and after the treatment trial was rated using three evaluation systems: (1) the Kurtzke disability status scale (DSS),[13] (2) a quantitative neurologic exam (QE),[13] and (3) the ambulation index (AI).[14] The course before entry was assessed by reviewing records of examinations by us or referring physicians. Only patients with documented deterioration in the year before entry were accepted into the study. All patients were examined immediately before entry and before each dose by two treating physicians (C.T.B. and D.E.M. or E.N. and A.M.S.). A third physician, not involved in patient management, also examined each patient before entry and at 3- to 6-month intervals thereafter. The response to treatment was designated as improvement (gain of one or more point on either DSS or AI), stable (no change in DSS or AI), or worse (loss of one or more points on either DSS or AI). Treatment failure was defined as worsening sustained over at least 6 weeks in spite of continued treatment.

Treatment regimen. All patients were admitted to the Clinical Center at the NIH or Walter Reed Army Medical Center for drug infusion. Informed consent was obtained. Polyriboinosinic acid polyribocytidylic acid stabilized in poly-L-lysine and carboxymethylcellulose (poly ICLC), prepared as previously described,[15] were obtained from the National Cancer Institute, NIH,

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Table 1. Patient characteristics

Group*	Pt	Age/Sex	Disease duration (yrs)	DSS†	Disease activity‡
I	1	47 M	3	3	DSS 2 to 3
	2	38 F	9	6	AI 5 to 7
	3	29 F	7	7	AI 7 to 8
	4	45 F	16	9	DSS 6 to 9
	5	41 F	2	8	DSS 6 to 8
	6	57 M	2	3	DSS 0 to 3
	7	35 M	19	3	DSS 0 to 3
	8	33 F	5	6	DSS 4 to 6
	9	23 M	4	6	DSS 3 to 6
II	10	34 M	9	6	−QE
	11	36 F	5	3	"
	12	48 M	20	6	"
	13	42 F	16	8	"
	14	27 F	5	9	"
	15	23 F	5	9	"
	16	35 M	11	3	"
	17	39 M	6	5	"
	18	46 M	14	7	"

* Group I = rapidly progressive with worsening of DSS or AI in the year before entry.
Group II = slowly progressive with worsening on examination only in the year before entry.
† Disability status score.[13]
‡ Activity in the year before entry (AI = ambulation index[14]; −QE = worsening in quantitative neurologic examination only).

Table 2. Acute side effects of poly ICLC drug infusion

	Percent of 263 infusions	Number of patients
Peak temp. over 37.5 °C	81	18
Transient elevated SGOT, SGPT	84*	10*
Nausea	75	18
Diffuse headache	57	15
Transient increased weakness	46	11
Vomiting	16	8
Transient recurrence of scotoma	9	3
Peak temp. over 40°C	5	9
Back pain	4	3
Transient quadriparesis	2	4
Vascular headache	2	3
Urinary retention	2	3
Prolonged elevation of SGOT, SGPT	1	3
Hives	1	2

* Only 127 infusions studied in 10 patients.

Bethesda, MD, in 10-mg vials, and diluted in normal saline immediately before use. Three different lots of drugs that were indistinguishable in side effects and IFN responses were used. The drug was administered as a slow IV infusion for 30 to 60 minutes, starting with a dose of 20 μg/kg, and was gradually increased to 100 μg/kg (tenfold less than the dose associated with hepatic and renal toxicity in some cancer patients treated in earlier trials). Weekly infusions were given for 6 to 12 weeks, followed by biweekly or monthly infusions for up to 18 months. To ameliorate fever and nausea, all patients received acetaminophen and perchlorperazine before each dose and for 24 to 48 hours after. A cooling blanket was used to treat fever over 37.5 °C.

Laboratory studies. Blood was taken for CBC, serum electrolytes, serum hepatic enzymes, blood urea nitrogen, creatinine, and immunoglobulins before each drug infusion. Blood was taken every 4 hours after drug infusion for determinations of serum IFN and cortisol. As previously reported,[16] serum IFN levels were determined[17] by the cytopathic effect reduction method on human foreskin fibroblast cells infected with vesicular stomatitis virus, using as a reference IFN, the National Institute of Allergy and Infectious Diseases reagent, catalog # 6023901537, and expressed in international units.

Results. *Acute side effects and drug toxicity.* Acute side effects varied widely from patient to patient and from dose to dose (table 2). During the infusion, six patients had transient symptoms including nausea, low back pain, and rhinitis. Two had hives that resolved when the infusion was stopped and did not recur with rechallenge. Most patients had no symptoms until 3 to 6 hours after infusion when fever, chills, nausea, headache, myalgia, and arthralgia began. Some patients noted neurologic worsening just before their temperature rose. Increased weakness and spasticity were seen frequently, and transient recurrence of resolved scotomata was seen in three patients. Rapid temperature elevation to over 40 °C was followed by transient quadriparesis, lasting 30 to 60 minutes, in four infusions. Three patients required intermittent catheterization for urinary retention. The duration of neurologic worsening was related both to the magnitude of fever and initial severity of neurologic signs. Patients with mild manifestations recovered from acute side effects within 48 hours, whereas those with severe disability (DSS 7, 8, or 9) required up to 5 days to regain strength. Side effects were responsible for the withdrawal of four patients early in the trial (table 3, # 14, #15, #16, and #17) and led to routine use of acetaminophen and perchlorperazine.

Polymorphonuclear leukocytosis and lymphocytopenia was seen in all 173 infusions studied. Transient slight elevation of SGOT and SGPT was seen in 84% of 127 infusions, but increased LDH or alkaline phosphatase was seen in only 52%. SGOT, SGPT, or LDH was high for more than 7 days in two patients. Drug was withheld until enzymes returned to normal, and elevations did not recur with rechallenge. Serum cortisol showed modest (25 to 40 IU/ml) elevations at 4 hours in all of 194 instances examined, with a return to normal diurnal variation in 24 hours.

One death occurred in a patient (table 3, # 18) who

Table 3. Responses t treatment

Group*	Pt	Treatment duration	Treatment response†	Treatment failure‡	Follow-up
I	1	18 months	Improvement (DSS 3 to 1)		Worse
	2	18 months	Improvement (AI 7 to 3)		Exacerbation
	3	18 months	Improvement (AI 8 to 7)		Stable
	4	18 months	Improvement (AI 9 to 8)		Stable
	5	18 months	Improvement (DSS 8 to 6)	15 months	Worse
	6	10 months	Stable		Worse
	7	18 months	Stable		Stable
	8	18 months	Stable	5 months	Stable
	9	7 doses	Worse (DSS 6 to 7)	2 weeks	Worse
II	10	18 months	Stable		Stable
	11	12 months	Stable		Stable
	12	13 doses	Stable		Stable
	13	10 doses	Stable		Stable
	14	3 doses	Withdrew		
	15	2 doses	Withdrew		
	16	2 doses	Withdrew		
	17	2 doses	Withdrew		
	18	2 doses	§		

* I = rapidly progressive.
II = slowly progressive.
† Improved = improvement of at least one point on either DSS or AI.
Stable = no change in either DSS or AI.
Worse = loss of at least one point on either DSS or AI.
‡ Treatment failure = worsening in spite of continued treatment for more than 6 weeks.
§ Died, unrelated to therapy.

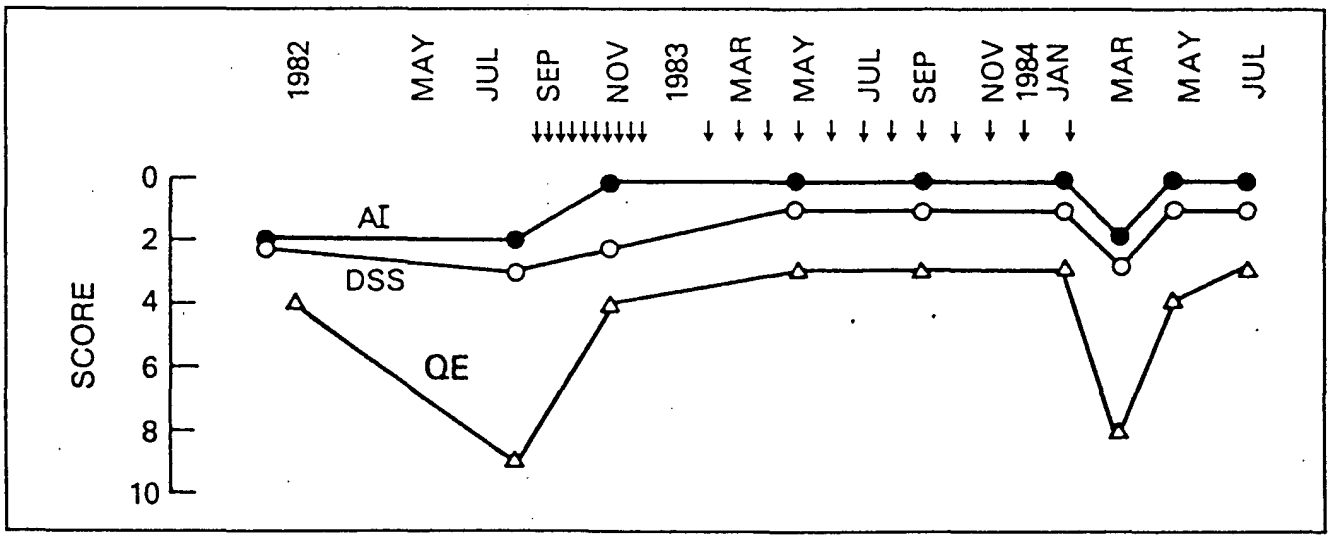

Figure 1. The clinical course of patient 1 showing DSS ○——○, AI ●——●, and QE △——△ scores. Arrows indicate poly ICLC infusions.

had been wheelchair-bound but began walking several days after his first dose of poly ICLC. Twenty-four hours after the second dose of poly ICLC, the patient had a fatal pulmonary embolism. A review of this death by the FDA concluded that it was not drug-related.

Interferon induction. Serum IFN levels were assayed after 194 infusions in the 10 patients treated in the Clinical Center of the NIH. All had peak levels between 8 and 12 hours after drug infusion with levels over 50 IU/ml in 82% and levels over 500 IU/ml in 15%. There was a general correlation between peak IFN levels and severity of side effects.[18]

Clinical response to poly ICLC. Nine patients with rapidly progressive MS (table 3, group I) were treated. Four patients improved. In patient 1 (figure 1), improvement of visual acuity, proprioception, gait, handwriting, and ability to complete an 8-hour workday were noted. One month after completing the 18-month treat-

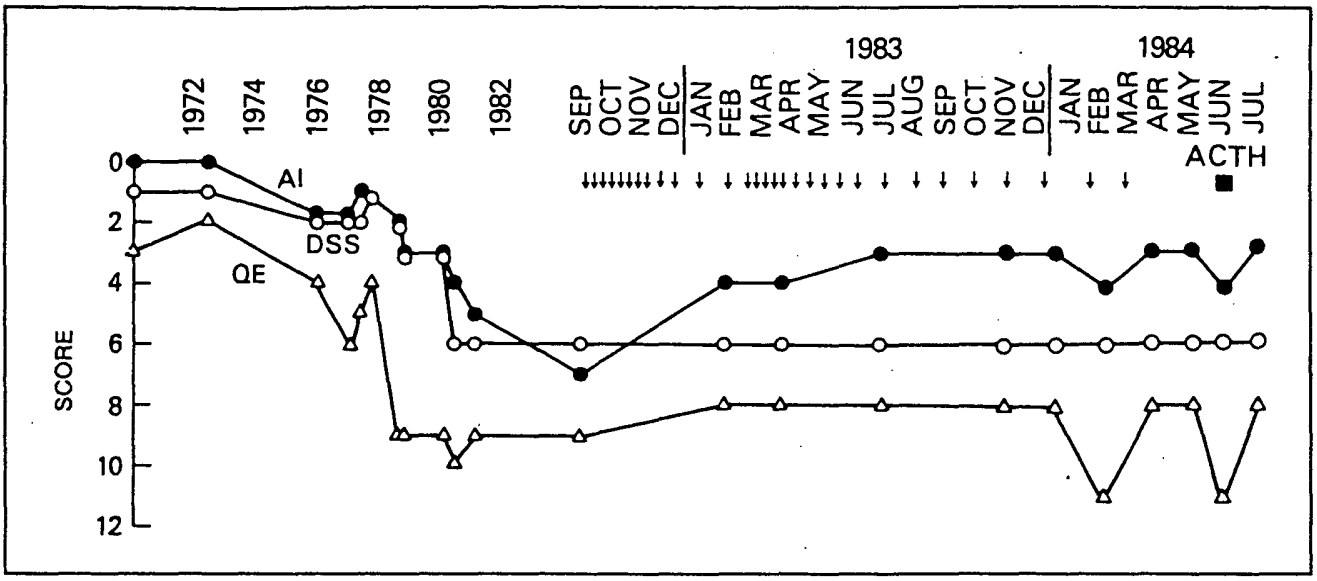

Figure 2. The clinical course of patient 2. Symbols as in figure 1. Solid bar indicates a course of ACTH.

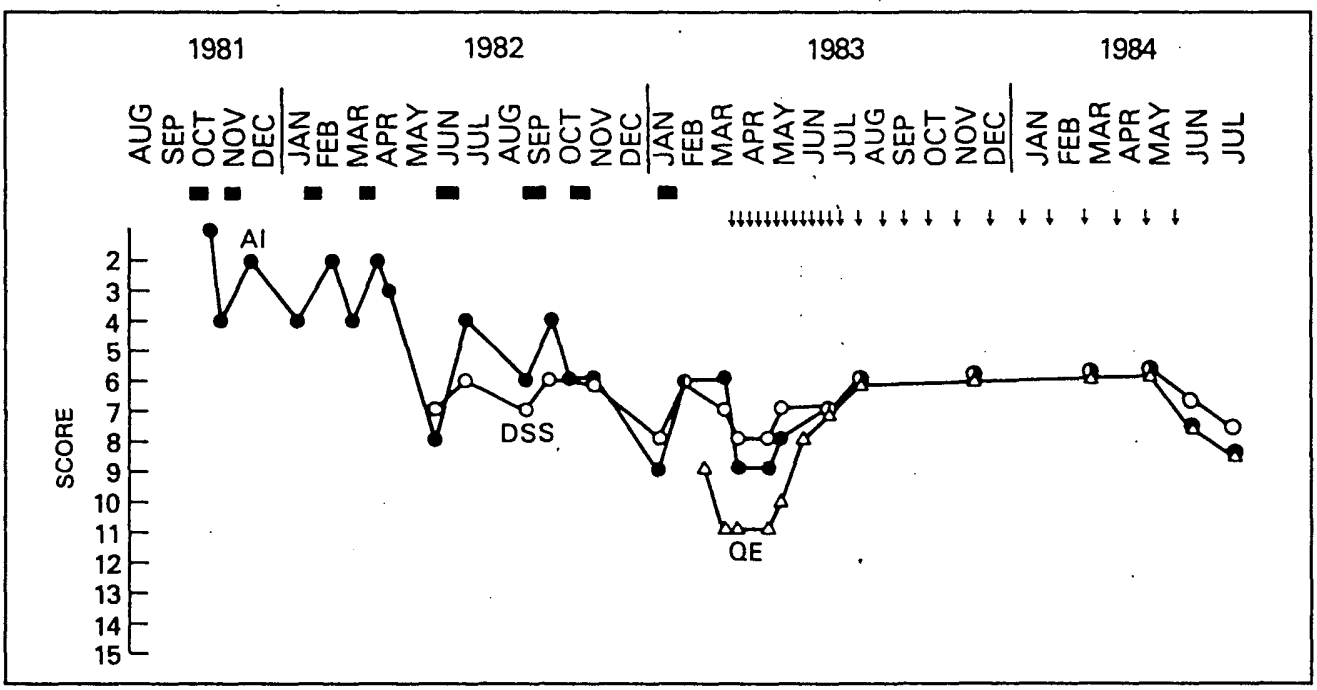

Figure 3. The clinical course of patient 4. Symbols as in figure 1. Solid bars indicate courses of ACTH.

ment period, he had an exacerbation followed by further worsening. Patient 2 (figure 2) had gradual improvement of walking over 8 months, followed by an exacerbation after 15 months with complete recovery. After completing the 18-month course, she had another exacerbation. Patient 3, who was initially wheelchair-bound, became able to take a few steps with assistance, and patient 4 had improvement of arm strength and coordination and became able to transfer independently. One patient (# 5) initially improved, but deteriorated on treatment (figure 3). Initially, she was wheelchair-bound. She had gradual improvement over 6 months and could walk 100 feet with a walker. However, after 15 months, she deteriorated in spite of continued treatment.

Two patients (# 6 and # 7) in group I stabilized on poly ICLC. Patient 6, who had progressive corticospinal disability, proprioceptive loss, and urinary retention, was stable during 10 months of treatment. He withdrew from the study to undergo surgery for a renal cell carcinoma and deteriorated neurologically after surgery. Patient 7 had progressive leg weakness, ataxia, and proprioceptive loss that did not progress during the 18 months of treatment. Patient 8, who had progressive spasticity, leg weakness, proprioceptive loss, and incontinence, stabilized for the initial 5 months on poly

ICLC, but then clearly deteriorated in spite of continued drug administration.

One patient in group I (# 9) continued to deteriorate. He had rapidly progressive spasticity, ataxia, sensory abnormalities, and required bilateral support to walk. Spasticity progressed during a 7-week course of poly ICLC infusions, and he could not walk when he withdrew from the study.

Nine patients with slowly progressive MS were treated (table 3, group II). Four (#10, #11, #12, and #13) remained stable during the treatment period and in follow-up. Four (#14, #15, #16, and #17) withdrew because of side effects after two or three doses each. One patient (#18) died, unrelated to therapy.

Discussion. In this preliminary trial of poly ICLC, the drug was used safely in patients with MS. Side effects included fever with temporary neurologic worsening, but later use of antipyretics kept fever at a level tolerated by most patients. The maximum usable dose was 100 μg/kg, and patients with advanced disability tolerated the drug less well. There was no lasting deleterious effect on MS patients.

We found substantial IFN responses. Diminished serum and CSF IFN levels have been reported in MS patients,[18] as well as defective IFN responses of peripheral blood mononuclear cells to various IFN inducers in vitro.[2] Whether the IFN responses in our MS patients were abnormal cannot be determined because no other patients undergoing poly ICLC treatment have been studied in comparable detail (H.B. Levy, unpublished observations). Poly ICLC can be used in MS patients to stimulate IFN levels, comparable with those seen when patients are given IFN systemically.

Because of the preliminary nature of this study, few conclusions about efficacy can be drawn. Poly ICLC did not cause deterioration in our patients. Although eight of nine patients with rapidly progressive MS stabilized or improved, one patient clearly showed no benefit, and two who initially stabilized or improved later worsened in spite of continued treatment. Whether these results show a partial beneficial effect, placebo effect, or the natural history of the disease cannot be resolved by this trial. Further study will be required to determine efficacy. Because acute side effects in MS patients were significant, drug use should be limited to settings allowing intensive monitoring and aggressive management. Patients with severe disability who did not tolerate fever well would not be good candidates for future trials. Because additional uncontrolled trials are unlikely to establish efficacy, a randomized, double-blind, controlled trial, which includes special provisions for maintaining and monitoring blinding, will be necessary.

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